REMARKS

A. Summary of the Invention

Broadly, the present invention concerns a reagent kit for detecting the presence or absence of one or more specific nucleotides at a predetermined target position in a target nucleic-acid polymer.

The reagent kit includes a detection primer comprising a detection-primer nucleotide sequence having a primer-extension-initiation 3'-end nucleotide which constitutes a 3' terminal end of the detection primer. The detection-primer nucleotide sequence is complementary to a primer-hybridizing nucleotide sequence of the target nucleic-acid polymer with a nucleotide in the target nucleic-acid polymer complementary to the primer-extension-initiation 3'-end nucleotide of the detection-primer nucleotide sequence defining a primer-end complement nucleotide. The primer-hybridizing nucleotide sequence of the target nucleic-acid polymer extends towards the 3' end of the target polymer from the primer-end complement nucleotide. The primer-end complement nucleotide is located in the target polymer at a position 3'-ward of the predetermined target position. The position of the primer-end complement nucleotide is subject to a constraint that no nucleotide of the same type as the one or more specific nucleotides to be detected be located in the target polymer in any position between the position of the primer-end complement nucleotide and the predetermined target position.

The reagent kit of the invention further includes an enzymatic polymerizing agent.

The reagent kit of the invention also includes a plurality of nucleoside triphosphates. In a first aspect, the plurality of nucleoside triphosphates includes at least one deoxynucleotide and at least two chain-terminating nucleotide analogues. At least one deoxynucleotide in such first aspect comprises a detectable label or an attachment moiety capable of binding a detectable label. In a second aspect, the plurality of nucleoside triphosphates includes at least one deoxynucleotide and at least one chain-terminating nucleotide analogue. At least one chain-

terminating nucleotide analogue in such second aspect comprises a detectable label or an attachment moiety capable of binding a detectable label. In both aspects, each deoxynucleotide of the plurality of nucleoside triphosphates is complementary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of the plurality is complementary.

In use, the detection primer of the reagent kit of the invention can hybridize to the target nucleic-acid polymer at the primer-hybridizing nucleotide sequence and form a detection-primer extension product by an enzyme-catalyzed primer-extension reaction to permit the presence or absence of a specific nucleotide at the predetermined target position to be detected by detecting the presence or absence of a corresponding detectable label in association with the detection-primer extension product.

B. Summary of the Outstanding Office Action

The attorneys for the applicants note with appreciation that claims 107 through 116 and 118 were allowed in the Office Action of 24 January 2005.

In the outstanding Office Action, claims 97 through 106 and 117 were rejected as unpatentable over United States patent No. 5,221,518 to Mills ("the Mills '518 patent") in view of European published patent application EP 0 297 379 to Dattagupta ("the Dattagupta '379 European published application"). With regard to the rejection of claims 97 through 106 and 117 in the Office Action, it was asserted that the Mills '518 patent disclosed methods for sequencing DNA involving use of a primer, a polymerase, and an admixture comprising labeled A, T, C, and G deoxynucleotides and A, T, C, and G chain-terminating nucleotide analogues. Columns 26, 36, 54, and 55 of the Mills '518 patent were cited in this regard. It was asserted that the method of the Mills '518 patent permitted a nucleotide sequence to be determined at a position immediately adjacent to or a plurality of nucleotides away from the 3' terminus of the primer. In the outstanding Office Action, it was noted that the rejected claims recited kits which contained chain-terminating nucleotide analogs and it was stated that the claims were considered to include

chain-terminating nucleotides which were labeled with a radioactive, mass, or fluorescent label. It was conceded in the Office Action of 24 January 2005 that the Mills '518 patent did not disclose packaging reagents required to practice the sequencing method of the patent in a kit. It was asserted in the Office Action that the Dattagupta '379 European published application disclosed packaging reagents such as primers, nucleotides, and polymerizing enzymes in a kit. It was asserted that it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have packaged a primer, polymerizing agent, and an admixture of labeled dNTPs and at least two different chain-terminating nucleotide analogs in a kit for assertedly expected benefits of convenience and cost-effectiveness for practitioners wishing to perform the disclosed method of sequencing target nucleic acids.

C. Summary of the Present Amendments and Request for Reconsideration

Independent claims 97 and 107 have been amended in the present response to substitute -- a plurality of nucleoside triphosphates -- in section (c) of the claims for "an admixture of nucleoside triphosphates." New claims 119 and 120 dependent respectively on independent claims 97 and 107 have been added in the present response to specify that the plurality of nucleoside triphosphates of the reagent kit of each of the respective parent independent claims as amended are packaged as an admixture. The amendments to claims 97 and 107 and new claims 119 and 120 regarding the plurality of nucleoside triphosphates of the claimed reagent kits find support in the application as filed at, for example, page 20, lines 24 through 27. It is submitted therefore that amendments to claims 97 and 107 regarding the plurality of nucleoside triphosphates of the claimed reagent kits and new claims 119 and 120 do not constitute new matter.

The conclusion of paragraph (c) of independent claim 97 has been amended above to specify that each deoxynucleotide of the plurality of nucleoside triphosphates of the reagent kit of the claim be complementary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of the plurality is complementary. The amendment to the

conclusion of paragraph (c) of claim 97 finds support in substance, if not *in haec verba*, at page 18, line 26 through page 19, line 22 of the application as filed, for example. It is submitted therefore that the amendment to the conclusion of paragraph (c) of claim 97 set forth above does not constitute new matter.

Reconsideration of the subject application as amended above in light of the comments below is respectfully requested.

D. The Rejections Under 35 U.S.C. § 103

Although the Mills '518 patent at column 3, lines 7 through 13 purported to have disclosed "a method of sequencing DNA," as best the undersigned attorney can understand the patent, it appears that with certain types of sequences, the information obtained using the method of the patent strictly as specified in the specification of the patent was insufficient to permit identification of which one of a plurality of different sequences was the actual sequence from which the information was obtained. The method of the Mills '518 patent involved a multistage process of generating from each segment of DNA to be sequenced a hierarchical family of individually-collected, dual-RNA/DNA polynucleotides, with each polynucleotide having an RNA portion forming the 5'-end of the polynucleotide followed by a DNA portion forming the 3'-end of the polynucleotide. As disclosed at column 3, lines 15 through 26 of the patent, each hierarchical family of polynucleotides was to be made up of a longest polynucleotide and a set of progressively shorter polynucleotides, each of which shorter polynucleotide was to be one nucleotide shorter – at either the RNA 5'-end or the DNA 3'-end – than a preceding polynucleotide in the family, but otherwise of the same sequence as the preceding polynucleotide. As specified at column 3, lines 26 through 36 of the '518 patent, each polynucleotide of a given hierarchical family was to include a common RNA/DNA dinucleotide which defined an "axis" for the family dividing the RNA portion from the DNA portion – although, inconsistently with the specification at column 3, lines 26 through 36, certain examples in the patent included in a hierarchical family of the example the single DNA nucleotide of the

RNA/DNA dinucleotide defining the so-called axis of the family. See, for example, Examples 1 and 2 extending between column 16, line 30 and column 17, line 22 of the patent. Although it is stated broadly at column 3, lines 57 through 61 of the '518 patent that the sequence of the DNA segment from which the corresponding hierarchical family of polynucleotides was generated could be determined by determining the respective total numbers of the different bases A, T, C, and G in each individual polynucleotide in the family, together with determining the identity of the 3'-terminal base of the polynucleotide, it appears that in certain cases such information must be supplemented with extrinsic knowledge about the specific sequence in order to identify which one of a plurality of different *a priori* equally-likely sequences was the actual sequence from which the information was obtained if each member of the hierarchical family of polynucleotides included the RNA/DNA dinucleotide axis as expressly specified at column 3, lines 26 through 36 of the specification of the patent. It is submitted that, in view of the apparent inconsistency between the method of the Mills '518 patent as expressly specified in the specification of the patent and examples set out in the specification of the patent, a person of ordinary skill in the art as of the effective filing date of the subject application would have to have exercised inventive faculties merely to divine if the '518 patent disclosed any method which could be used to sequence DNA as purported in the patent. It is submitted therefore that, at the relevant time, the Mills '518 patent would not have identified a set of reagents which a person of ordinary skill in the art without the exercise of inventive faculties would have recognized could be used for the purpose of sequencing DNA as purported in the patent as asserted in the outstanding Office Action in connection with the rejection of claim 97 under 35 U.S.C. § 103.

Moreover, as amended above, claim 97 calls for a reagent kit which comprises a plurality of nucleoside triphosphates including at least one deoxynucleotide and at least two different chain-terminating nucleotide analogues wherein each deoxynucleotide of the plurality of nucleoside triphosphates is specified to be complementary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of the plurality of nucleoside triphosphates is complementary. In contrast, the reagents disclosed in the Mills '518 patent at

column 26, lines 5 through 18 – whatever the ultimate use a person of ordinary skill in the art without the exercise of inventive faculties could have divined such reagents might be put – included labeled A, T, C, and G deoxyribonucleotides and labeled A, T, C, and G dideoxyribonucleotides and thus each deoxyribonucleotide included in the reagents would have necessarily been complementary to a nucleotide to which one of the dideoxyribonucleotides included in the reagents was complementary.

For the reasons set forth above, it is submitted that the Mills '518 patent would have neither disclosed nor suggested the subject matter of claim 97, particularly as amended herein, to a person of ordinary skill in the art as of the effective filing date of the subject application.

The Dattagupta '379 European published application does not cure the infirmities of the Mills '518 patent as a reference against claim 97 of the subject application as amended. It is submitted, therefore, that the Mills '518 patent considered alone or in combination with the Dattagupta '379 European published application would have neither disclosed nor in any way suggested the reagent kit of claim 97 as amended to a person of ordinary skill in the art as of the effective filing date of the subject application. The rejection of amended claim 97 under 35 U.S.C. § 103 as unpatentable over the Mills '518 patent in view of the Dattagupta '379 European published application is without justification, it is submitted, and should be withdrawn.

Claims 98 through 106 inclusive, 117, and new claim 119 of the application are dependent claims which depend upon independent claim 97 as amended and consequently incorporate the limitations of amended claim 97 by reference. The reasoning set forth above concerning distinctions between the Mills '518 patent considered alone or in combination with the Dattagupta '379 European published application and the reagent kit of claim 97 as amended therefore applies with equal force with respect to dependent claims 98 through 106 inclusive, 117, and 119. Consequently, it is submitted that the Mills '518 patent considered alone or in combination with the Dattagupta '379 European published application would have neither

disclosed nor in any way suggested the subject matter of claims 98 through 106 inclusive, 117, and 119 to a person of ordinary skill in the art as of the effective filing date of the subject application. It is submitted, therefore, that the rejection under 35 U.S.C. § 103 of dependent claims 98 through 106 inclusive and 117 of the subject application as amended as unpatentable over the Mills '518 patent in view of the Dattagupta '379 European published application is without justification and should be withdrawn. Likewise, it is submitted that a rejection of new claim 119 – as well similarly as new claim 120 – as unpatentable over the Mills '518 patent considered alone or in combination with the Dattagupta '379 European published application would be without basis.

For the reasons set forth above, it is submitted that the rejection under 35 U.S.C. § 103 of claims 97 through 106 inclusive and 117 of the subject application as amended as unpatentable over the Mills '518 patent in view of the Dattagupta '379 European published application is unwarranted and should be withdrawn. It is further submitted that a rejection of either of new claim 119 or 120 as unpatentable over the Mills '518 patent considered alone or in combination with the Dattagupta '379 European published application would be unjustified.

E. Conclusion

For the reasons set forth above, it is submitted that the claims of the subject application as amended are patentable over the art of record considered alone or in any combination. Early allowance of the application is therefore earnestly solicited.

Respectfully submitted,

Attorneys for the Applicants

by _____
J. David Ellett, Jr. (Reg. No. 27,875)

Telephone No.: (212) 813-1600